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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/728,291	12/04/2003	Stephen F. Badylak	3220-73986	7088

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EXAMINER	
FORD, ALLISON M	

ART UNIT	PAPER NUMBER
1651	

NOTIFICATION DATE	DELIVERY MODE
03/12/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

indocket@btlaw.com

Office Action Summary	Application No.	Applicant(s)	
	10/728,291	BADYLAK ET AL.	
	Examiner	Art Unit	
	ALLISON M. FORD	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 December 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *9-24* is/are pending in the application.

4a) Of the above claim(s) *17-24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/19/2008 has been entered.

Claim 9 has been amended; claims 1-8 have been cancelled. Claims 9-24 remain pending in the current application, of which claims 17-24 remain withdrawn from consideration pursuant to 37 CFR 1.142(b), as being directed to a non-elected invention. Claims 9-17 have been considered on the merits.

Response to Arguments

Applicants' arguments of 12/19/2008 have been fully considered. Each argument will be addressed below as appropriate. Rejections/objections not repeated herein have been withdrawn from consideration.

All rejections to claims 1-8 are rendered moot due to their cancellation.

With regards to the rejection of claims 9-16 as being obvious under 35 USC 103(a), Applicants assert that the Examiner has not established a proper *prima facie* case of obviousness, yet even if such a case was made, Applicants assert the rejections are overcome by a showing of unexpected results.

Applicants have not set forth reasons why the rejection of record fails to set forth a proper *prima facie* case of obviousness, thus the comments will be limited to the assertions of unexpected results. Applicants have reiterated their previous argument that the liver basement membrane used in the current

method provides the unexpected result of being capable of maintaining functional hepatocytes in culture, whereas the prior art only suggested the liver basement membrane composition could support and stimulate hepatocyte proliferation. Applicants stress that hepatocyte proliferation does not necessarily equate to maintenance of hepato-cellular function, whereas the hepato-cellular functions, now recited in the claims, are selected from the group consisting of albumin production, urea production, and cytochrome P450 activity. Applicants assert the maintenace of hepato-cellular functionality in *in vitro* cultures was not routine prior to the current invention, and assert their liver basement membrane supported superior functionality as compared to collagen-adsorbed collagen. Applicants further traverse the Examiner's reliance on the showings of Yamamato et al, Wang et al and Campbell et al as showing maintenance of hepatocyte functionality in *in vitro* culture on the grounds that each of these references were made available after the earliest priority of the instant application (Dec 2002).

Applicant's arguments have been fully considered, but are not found persuasive. It is maintained that means were known in the art, at the time the instant invention was made, to culture hepatocytes such that they maintain their functionality (functionality selected from the group consisting of albumin production, urea production and cytochrome P450 activity), in support, the teachings of Naughton et al have been incorporated into the rejection. Naughton et al teach hepatocytes can be cultured *in vitro* while retaining their functionality by co-culturing the hepatocytes with stromal cells. Thus, Applicants arguments as to the capability of hepatocytes to maintain functionality being unexpected are unpersuasive, as Naughton et al, available well before the filing date of the instant invention, shows such means were possible, and as such, these means could have been employed in the culture of hepatocytes on the liver basement membrane disclosed by Badylak, and the resulting graft implanted into a patient in need thereof with a reasonable expectation of retaining the hepato-cellular functions and repairing damaged or diseased liver tissue.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 9-16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 9 is considered indefinite because it comprises two 'administering' steps: in line 3 and in line 8. The metes and bounds of the claimed method are unclear due to the duplicity of the steps.

Furthermore, in claim 9 the first administering step has a caveat that "the liver basement membrane *is* seeded with hepatocytes for a time sufficient to allow said hepatocytes to grow," this limitation is unclear as to whether the administering step further comprises a step *of* seeding the hepatocytes onto the liver basement membrane, or if the claim is intending to define the liver basement membrane as *having been* seeded with hepatocytes. Clarification is required.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 9-16 are rejected under 35 U.S.C. 103(a) as being obvious over each of Badylak WO 98/25637 and Badylak US Patent 6,793,939 (national stage entry of PCT/US97/22727), each in view of Naughton et al (US Patent 5,510,254).

It is noted the applied **patent** reference (US 6,793,939) has a common inventor and assignee with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). This rejection might also be overcome by showing that the reference is disqualified under 35 U.S.C. 103(c) as prior art in a rejection under 35 U.S.C. 103(a). See MPEP § 706.02(l)(1) and § 706.02(l)(2). Please note the WIPO publication is prior art under 35 USC 102(b) and cannot be overcome in such a manner.

In each reference Badylak disclose methods of inducing endogenous tissue formation at a site in need thereof by administering a graft composition comprising liver basement membrane in an amount effective to induce the repair of the tissue at the site of administration. Badylak disclose the graft composition can be administered as a multi-layered composition formed from two or more layers of liver basement membrane (See WO 98/25637 Pgs 8-9/ See USP '939 col. 6, ln 13-64). The thickness of individual layers/sheets would be routinely optimized to suit the intended implantation site's needs (size and shape). Badylak further state the basement membrane can be provided in various forms, including a fluidized liquid (which can also be considered a gel) or powder form (See WO 98/25637 Pg. 4-5/ See USP '939 col. 3, ln 45-col. 4, ln 11).

Badylak further disclose eukaryotic cells may be seeded onto the liver basement membrane prior to implantation to enhance the tissue replacement capabilities of the graft material upon administration. Cells corresponding to the target tissue site (target tissue site being the site to which the graft is being administered to induce endogenous tissue formation) may be cultured on the liver basement membrane material, and the graft then implanted to the corresponding target tissue site. For example, Badylak discloses culturing keratinocytes on liver basement membrane for use as a skin graft, or culturing endothelial cells on liver basement membrane for use as a vascular graft. Badylak further discloses other cell types, including hepatocytes, may be cultured on the liver basement membrane (See WO 98/25637 Pg 12/ See USP '939 col. 8, ln 30-col. 9, ln 23).

Badylak differs from the instant method in that, while he suggests producing a graft material comprising liver basement membrane with hepatocytes cultured thereupon, he does not disclose administering such a graft for use as a liver tissue graft to repair damaged or diseased liver tissue. Badylak further differs in that he does not report on the functionality of the hepatocytes once cultured on the liver basement membrane.

However, at the time the invention was made the need for a method of repairing damaged or diseased liver tissue was well recognized, and thus the artisan of ordinary skill would have been motivated to adapt the method of Badylak to include administering a hepatocyte-containing liver basement membrane graft material to a patient in need thereof in order to solve the recognized need in the art.

It is understood that hepatocytes can quickly loss their functionality during *in vitro* culture; however Naughton et al disclose that by co-culturing hepatocytes with stromal cells, the hepatocytes maintain their functionality (See Naughton et al, col. 6, ln 51-col. 8, ln 34), wherein the functionality

includes albumin production (See Naughton et al, Fig. 4A), cytochrome P450 activity (See Naughton et al, Fig. 5B), and even urea production (See Naughton et al, col. 17, ln 65-col. 18, ln 5).

Therefore, it would have been well within the purview of one of ordinary skill in the art, at the time the invention was made, to employ the co-culture technique of Naughton et al in the method of Badylak, thereby arriving at a method where hepatocytes and stromal cells may be co-cultured on the liver basement membrane to produce a liver tissue graft that may be administered to a patient in need of liver repair. Based on the disclosure of Naughton et al, regarding the maintained functionality of the hepatocytes in co-culture, one would have had a reasonable expectation that the hepatocytes would retain their tissue-specific functions, including albumin production, urea production and cytochrome P450 activity, thereby repairing and/or augmenting damaged or diseased liver tissue.

Therefore the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 9-16 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-14 of U.S. Patent No. 6,793,939, in view of Badylak (WO 98/25637), and further in view of Naughton et al (US Patent 5,510,254).

The patented claims disclose methods of inducing the formation of endogenous tissue at a site in need thereof by implanting a graft composition comprising the same liver basement membrane as disclosed in the current claims; the patented claims differ in that they do not specify the liver as the endogenous tissue in need of repair, and they do not disclose hepatocytes being present on the liver basement membrane.

However, Badylak (WO 98/25637), which discloses the same liver basement membrane material for implantation to repair damaged tissue, disclose eukaryotic cells may be seeded onto the liver basement membrane prior to implantation to enhance the tissue replacement capabilities of the graft material upon administration. Badylak discloses hepatocytes amongst the cells that may be cultured on the liver basement membrane (See WO 98/25637 Pg 12).

Furthermore, as discussed above, Naughton et al discloses co-culturing hepatocytes with stromal cells maintains hepato-cellular tissue-specific functions, including albumin production, urea production and cytochrome p450 activity.

Therefore, though the current claims and the patented claims are not identical, they are not considered patentably distinct, because it would have been obvious to one of ordinary skill in the art to improve upon the patented method by including tissue-specific cells on the liver basement membrane material, as suggested by Badylak, and further including stromal cells so as to maintain the functionality of the hepatocytes in culture, as suggested by Naughton et al.

Claims 9 and 12 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 3, 12 and 14 of U.S. Patent No. 7,482,025, in view of Badylak (WO 98/25637), and further in view of Naughton et al (US Patent 5,510,254).

The patented claims disclose methods of inducing the formation of endogenous tissue at a site in need thereof by implanting a graft composition comprising the same gelled liver basement membrane as disclosed in the current claims, and with endogenous cells cultured thereupon; the patented claims differ in that they do not specify the liver as the endogenous tissue in need of repair, and they do not disclose hepatocytes as the specific cell type cultured thereupon.

However, Badylak (WO 98/25637), which discloses the same liver basement membrane material for implantation to repair damaged tissue, disclose eukaryotic cells may be seeded onto the liver basement membrane prior to implantation to enhance the tissue replacement capabilities of the graft material upon administration. Badylak discloses hepatocytes amongst the cells that may be cultured on the liver basement membrane (See WO 98/25637 Pg 12).

Furthermore, as discussed above, Naughton et al discloses co-culturing hepatocytes with stromal cells maintains hepato-cellular tissue-specific functions, including albumin production, urea production and cytochrome p450 activity.

Therefore, though the current claims and the patented claims are not identical, they are not considered patentably distinct, because it would have been obvious to one of ordinary skill in the art to improve upon the patented method by including tissue-specific cells on the liver basement membrane material, as suggested by Badylak, and further including stromal cells so as to maintain the functionality of the hepatocytes in culture, as suggested by Naughton et al.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ALLISON M. FORD whose telephone number is (571)272-2936. The examiner can normally be reached on 8:00-6 M-Th.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Allison M. Ford/
Examiner, Art Unit 1651